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Effects of Protracted Ionizing Radiation Dosage on Humans and Animals: A Brief Review of Selected Investigations

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13. ABSTRACT *(Maximum 200 words)*

A review of selected investigations of animal irradiation studies, radiation therapy experience, and radiation accident accounts is presented, and some acute effects of protracted ionizing radiation exposure on animals and humans are discussed. Various guidelines and models, which account for biological recovery when radiation exposure is protracted over time, are compared.

Biological response modifying effects of dose rate and protraction period in humans are discussed in terms of prodromal symptoms. Radiation injury and recovery in a variety of animals, based on the LD_{50} endpoint, are reviewed and summarized for low and high dose rates ranging from 0.5 to about 700 R/h. Biological recovery models and guidelines are empirical and are primarily based on radiation injury accumulation in animals and gauged by the LD_{50} endpoint.

Further development of appropriate protracted dose models is relevant and necessary for military operations and emergency civil defense planning.

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SUMMARY

Net radiation injury is significantly lowered, as dose rate is decreased, by biological repair and recovery mechanisms. This report, based on a brief review of selected radiobiological literature, illustrates that effect. In a postnuclear weapon attack environment, where fallout radiation lingers, military operations and emergency civil defense activities could be significantly impacted depending on whether or not recovery from radiation injury is taken into account. Since current U.S. military training doctrine generally makes no distinction between prompt and protracted radiation exposure effects, the need to provide a more comprehensive basis to make such a distinction is emphasized. This effort provides an initial step by briefly reviewing the kinds of information that can usefully serve that end.

The results of selected radiobiological investigations highlighted here, demonstrate the modifying effects of protracted radiation exposure (as compared to prompt exposure) in humans and animals. Included are radiation-induced human prodromal responses following nuclear accidents and radiation therapy, and radiation injury and recovery data from radiation fatality studies performed with animals.

Acute prodromal effects such as anorexia, nausea, and vomiting are virtually nil for dose rates less than about 1 rad/h. However, bicycle/ergonometry tests reveal fatigability for exposure at that level, both for continuous exposure over 5 days or daily fractions of 10 R, when the dose accumulates to 150 R (approximately 100 rads midline in tissue).

Vomiting was noted in ten percent of people accidentally exposed to fallout from tests in the Pacific; the dose rate was about 3 to 3.5 rads/h over an exposure period of about 50 h. For a much higher rate of about 60 rads/h, vomiting is estimated to be about 40 to 50 percent for the same total dose (175 rads). When the dose rate increases from a few rads per hour (≈ 3 rads/h) to about 10 rads/h, radiation is a factor of 2.2 to 2.5 more effective at producing vomiting. Beyond that dose rate range and up to the lower therapy

levels that have been employed (≈ 60 rads/h), very little human experience exists by which to gauge the occurrence of emesis. However, comparing the response of the therapy patients and accident victims exposed at high dose rates (> 60 rads/h), the onset and occurrence of prodromal symptoms appear to be more related to total dose than to dose rate.

Man's $LD_{50/60}$ response to protracted radiation exposure is thought to be similar to that in larger animals and significantly different from that in smaller ones. Of the larger animals, swine show the most pronounced recovery from protracted radiation injury. The LD_{50} for sheep (and probably for other larger animals as well) decreases linearly with exposure rates from about 30 to 700 R/h; from 700 to 2400 R/h, a limit is reached beyond which the LD_{50} becomes constant (i.e., no further recovery is observed). A pronounced increase in LD_{50} is observed beginning with dose rates of less than about 30 R/h. At dose rates of 0.5 and 0.95 R/h, and at least up to total doses of 165 R, complete recovery occurs in sheep. When the dose rate is increased to 1.85 and 3.9 R/h, there are residual injuries of 75 or 104 R, respectively. However, a continuous dose rate of about 1 R/h for an extended period of 30 days results in an injury accumulation rate between 0.19 to 0.25 R/h. Injury accumulates more rapidly in sheep at 3.6 R/h than at 1.9 R/h, given the same total dose.

Postirradiation recovery oscillates. In sheep, slow recovery up to about day 7 is followed by rapid recovery until about day 20. Beyond that and for a period of at least 75 days, residual injury is measured. Recovery in larger animals is not uniform in either magnitude or postirradiation time. Recovery is earlier in smaller animals than in larger ones, and only partial in primates. Sheep exposed to protracted doses appear to recover faster than those exposed to acute doses. The biological recovery capability of animals at low dose rates (3.8 R/h) decreases with the magnitude of an initial acute dose. This decreased recovery capability has been demonstrated in sheep for initial acute doses at higher dose rates (9.1 and 45 R at 575 R/h, and 155 R at 510 R/h).

Models and guidelines for protracted radiation exposure that have appeared in various publications are reviewed and compared. Modeling that has been performed and which takes into account the biological recovery and repair of radiation injury in complex organisms, is primarily based on research with animals ranging in size from the mouse to the burro. Limited data have also been derived from cancer patients undergoing radiotherapy and from radiation accident victims.

Considerably more attention has been given to the development of models for cell or specific tissue-level response than for the whole organism. Consequently, experts have achieved a much higher degree of focused consensus for modeling biological repair and recovery at the cell and tissue level than for the whole organism.

Because lethality (specifically, 50 percent lethality) represents an unambiguous response observed by the researcher, it is the endpoint most frequently chosen for animal studies. To illustrate biological recovery based on selected models, we employ the lethality endpoint in terms of the LD_{50} versus exposure dose rate. Although the LD_{50} endpoint per se is of obvious interest to military planners, its validity is questionable when it is applied globally to models of all manner of radiation injury recovery.

Plots of the protracted radiation response models show a considerable variation in accumulated lethal exposure dose versus dose rate. However, with the exception of the Bateman model, those plotted suggest a marked increase in LD_{50}, commencing with dose rates less than about 3 to 10 rads/h; a more rapid increase in LD_{50} for dose rates from about 1 to 3 rads/h probably reflects cell proliferation. Since the Bateman model is based on a relationship that follows an inverse proportionality with the cube root of dose rate, the log-log plot shows that, compared with the other models, the Bateman model yields a more gradual increase with decreasing dose rate. However, some of the differences between the models are due to the values assigned to the LD_{50} for prompt exposure or a period of brief exposure, reflected at the high dose rate end of the plots. We have, where possible, attempted to choose values that are consistent with discussions of the models in the literature.

Based on our brief review, models of protracted radiation response that use the lethality endpoint need further investigation. Even though lethality is only one of the endpoint responses of interest in casualty considerations, the models do predict various degrees of biological repair. We find here that both the Krebs and Jones model and the ERD model appear to be the most promising. The four-parameter Krebs and Jones model, although somewhat complex, is flexible and appears to simulate the expected trend of accumulated dose with decreasing dose rate as does the Bateman model; however, the ERD model has the disadvantage of being transcendental when dose rate is expressed as the independent variable.

Better substantiation of any selected model should be based on a more in-depth analysis of available data from animal studies and human experience; for example, the Juarez, Mexico, accident involving exposure to cobalt-60 γ-ray radiation from a discarded radiotherapy unit can yield still more information. Also, our comparisons of the protracted radiation exposure models here are based on continuous and constant exposure rate levels because data on arbitrary exposure periods and/or varying dose rates are scarce or limited in scope. However, as Krebs and Jones imply, when average daily dose rates are less than about 2.6 rads/h (or about 60 rads/day), the exposure history for the 24-h period is irrelevant.

Through further investigation, it should be decided whether utilizing the kinds of models reviewed here would be appropriate to express biological recovery for interrupted periods of exposure and time-varying dose rates.

Additional investigation is also required to choose whether the types of models presented here, or modifications of them, can be applied to other endpoints such as prodromal responses. Although it is unclear whether these models can adequately be applied to the prodromal symptomatology for protracted radiation, some studies have taken that approach. However, because the kind of biological recovery illustrated in this review may not adequately model other processes (such as the physiological clearing action, perhaps combined with repair), a different type of modeling approach may be necessary to

accommodate prodromal responses to protracted radiation. For example, for dose rates in the therapy range of about 1 to 30 rads/min (60 to 1800 rads/h), there are indications that nausea and vomiting depend more on the total accumulated dose than on the dose rate. This review of existing models of protracted radiation based on lethality as the endpoint reveals the need for further study, prior to development of a system analysis approach for application to military operations and planning.

PREFACE

Prior investigations of the biological effects of ionizing radiation supported by the Defense Nuclear Agency (DNA) have focused on prompt radiation exposure. Those investigations have mainly evolved under the DNA Intermediate Dose Program to provide technical support for U.S. Army education and training programs.

This report represents an initial subject review effort to extend the DNA investigations of biological effects to protracted radiation exposure such as that expected from a lingering radiation fallout environment following nuclear weapon detonation. This effort was performed under the guidance and direction of DNA staff member Dr. Robert W. Young, Science and Technology Radiation Policy Directorate (STRP).

CONVERSION TABLE

Conversion factors for U.S. Customary to metric (SI) units of measurement

MULTIPLY → TO GET	BY	TO GET ← DIVIDE
angstrom	1.000 000 X E -10	meters (m)
atmosphere (normal)	1.013 25 X E +2	kilo pascal (kPa)
bar	1.000 000 X E +2	kilo pascal (kPa)
barn	1.000 000 X E -28	meter^2 (m^2)
British thermal unit (thermochemical)	1.054 350 X E +3	joule (J)
calorie (thermochemical)	4.184 000	joule (J)
cal (thermochemical)/cm^2	4.184 000 X E -2	mega joule/m^2 (MJ/m^2)
curie	3.700 000 X E +1	*giga becquerel (GBq)
degree (angle)	1.745 329 X E -2	radian (rad)
degree Fahrenheit	t_k = (t°f + 459.67)/1.8	degree kelvin (K)
electron volt	1.602 19 X E -19	joule (J)
erg	1.000 000 X E -7	joule (J)
erg/second	1.000 000 X E -7	watt (W)
foot	3.048 000 X E -1	meter (m)
foot-pound-force	1.355 818	joule (J)
gallon (U.S. liquid)	3.785 412 X E -3	meter^3 (m^3)
inch	2.540 000 X E -2	meter (m)
jerk	1.000 000 X E +9	joule (J)
joule/kilogram (J/kg) (radiation dose absorbed)	1.000 000	Gray (Gy)
kilotons	4.183	terajoules
kip (1000 lbf)	4.448 222 X E +3	newton (N)
kip/inch^2 (ksi)	6.894 757 X E +3	kilo pascal (kPa)
ktap	1.000 000 X E +2	newton-second/m^2 ($N-s/m^2$)
micron	1 000 000 X E -6	meter (m)
mil	2.540 000 X E -5	meter (m)
mile (international)	1.609 344 X E +3	meter (m)
ounce	2.834 952 X E -2	kilogram (kg)
pound-force (lbs avoirdupois)	4.448 222	newton (N)
pound-force inch	1.129 848 X E -1	newton-meter (N·m)
pound-force/inch	1.751 268 X E +2	newton/meter (N/m)
pound-force/foot^2	4.788 026 X E -2	kilo pascal (kPa)
pound-force/inch^2 (psi)	6.894 757	kilo pascal (kPa)
pound-mass (lbm avoirdupois)	4.535 924 X E -1	kilogram (kg)
pound-mass-foot^2 (moment of inertia)	4.214 011 X E -2	kilogram-meter^2 ($kg \cdot m^2$)
pound-mass/foot^3	1.601 846 X E +1	kilogram/meter^3 (kg/m^3)
rad (radiation dose absorbed)	1.000 000 X E -2	**Gray (Gy)
roentgen	2.579 760 X E -4	coulomb/kilogram (C/kg)
shake	1.000 000 X E -8	second (s)
slug	1.459 390 X E +1	kilogram (kg)
torr (mm Hg, 0° C)	1.333 22 X E -1	kilo pascal (kPa)

*The becquerel (Bq) is the SI unit of radioactivity; 1 Bq = 1 event/s.
**The Gray (Gy) is the SI unit of absorbed radiation.

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SECTION 1
INTRODUCTION

In current U.S. military training doctrine, no distinction is made between the radiobiological effects of prompt and protracted ionizing radiation exposure. It has been clearly demonstrated however, that, as dose rate decreases, the mechanisms of biological repair and recovery significantly lower net radiation injury. Intermittent exposures, over increasing periods of time, have the same effect. The U.S. military should consider reduced radiation injury effect when dosage accumulates over an appreciable period of time. Military operations and planning could be impacted in areas where lingering fallout radiation is a significant source of radiation exposure after nuclear weapon detonation.

In this report, we present and discuss results derived from selected radiobiological literature that demonstrate the modifying effect of protracted, compared to prompt, radiation exposure in humans and large animals. Included are radiation-induced prodromal responses based on human experience and radiation-induced injury and recovery from fatality studies on animals.

SECTION 2
PRODROMAL SYMPTOM RESPONSE

It has been demonstrated that prodromal responses such as anorexia, nausea, vomiting, and fatigue represent reasonable biological endpoints by which to gauge the injurious effects of ionizing radiation exposure in humans [Langham, 1967; Lushbaugh, Comas, and Hofstra, 1967; and Lushbaugh et al., 1966]. Furthermore, the prodromal response symptomatology can be correlated with radiation exposure levels to provide a basis for inferring the extent of functional capability degradation expected in troops required to perform military tasks in a battlefield setting where nuclear weapons are employed [Anno, Wilson, and Dore, 1984].

Aside from dose level and individual response sensitivity, the rate and protraction history of radiation exposure can be expected to affect the degree, frequency, and timing of the prodromal responses [Lushbaugh, 1969; Lushbaugh et al., 1966; and Lushbaugh et al., 1968], which are of obvious interest to military planners. However, the lack of experience and research in dose rate or protracted radiation exposure effects on the prodromal response symptomatology has severely limited our confidence in the development of appropriate models or algorithms that can be applied to predict human performance capability. The lack of data is particularly pronounced for low-dose-rate exposures (less than several rads per hour), although a similar gap in information exists regarding response effects for dose rates up to several tens of rads per hour.

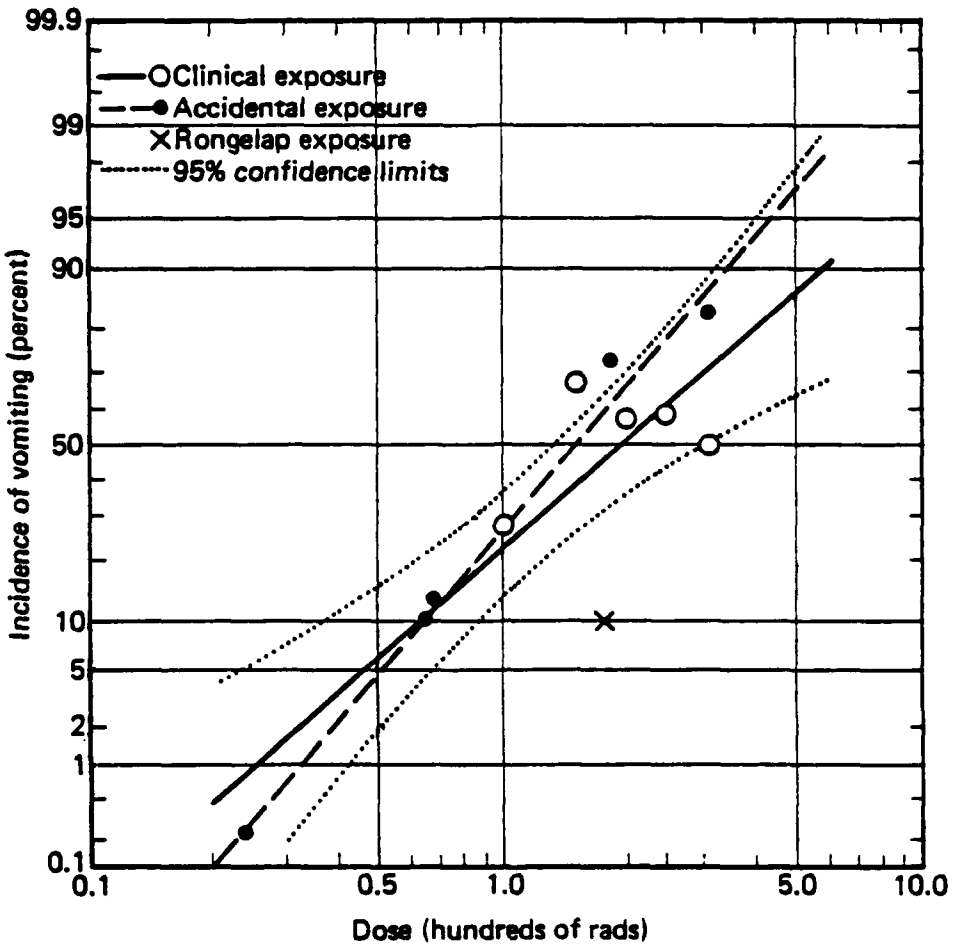
Early total body irradiation (TBI) treatments, where patients were exposed to about 1 to 1.5 rads/min (60 to 90 rads/h), provide some clinical experience that can be applied to the development of prodromal response modeling. Over the past decade or more, clinical advances in TBI treatment techniques have resulted in the common use of dose rates up to ≈ 30 rads/min (1800 rads/h) [Anno, Brode, and Washton-Brown, 1982]. The upper level of dose rate in prodromal response is derived from limited experience--accidents in which

victims were exposed to many thousands of rads in a fraction of a second [Baum et al., 1984]. However, a comparison of the onset time of prodromal symptoms (nausea and vomiting) to dose level did not show a marked difference between accident victims and TBI therapy patients exposed to between 60 and 1800 rads/h [Anno, Wilson, and Dore, 1984]. Furthermore, some radiation therapists and radiobiologists recently found no evidence of earlier onset or worse nausea or vomiting in therapy patients as dose rate was increased within the above therapeutic exposure range [Fliedner and Van Beckum, 1983; and Thomas, Dicke, and Santos, 1983].

HUMAN EXPERIENCE.

In Fig. 1 [Langham, 1967], probit analysis of the incidence of vomiting based on clinical data is shown by the solid line. The figure includes 95 percent confidence limits (dotted arcs). The dashed line represents the incidence of vomiting in 45 men accidentally exposed (separated into four average dose groups). The data points for accidental exposure to primarily high dose rates (probably thousands of rads per fraction of a second) fall within the fiducial limits determined from clinical data, where the exposure rate for 84 of 163 cases was ≈ 1.5 R/min (≈ 60 rads/h). Therefore, it can be argued that the two groups respond similarly to protracted radiation. That is, the incidence of vomiting may not significantly change at dose rates higher than several tens of rads per hour. Based on these data, it can also be argued that the response of normal men (the accident victims) is similar to that of clinical patients, albeit with less variation in response (indicated by the steeper slope of the dashed line) with respect to dose.

The isolated point marked "X" in Fig. 1 represents the vomiting incidence of 64 Marshallese (Rongelap natives) accidentally exposed to an estimated 175 rads of fallout radiation from a nuclear weapon test [Cronkite, Bond, and Dunham, 1956]. Dose rates were estimated to have ranged from about 5.5 rads/h at the beginning of exposure to about 1.6 rads/h at the end of exposure (when evacuation took place). The estimated range of average dose rate over an exposure of about 51 h



Source: Langham [1967].

Figure 1. Incidence of vomiting (within 2 days of dose) as function of dose assuming lognormal distribution of quantal response.

was about 3 to 3.5 rads/h. According to the accident and clinical data shown in Fig. 1, the same incidence of vomiting (10 percent at 175 rads total dose for the Marshallese) would occur at a lower total dose of about 65 rads if the dosage were delivered at a much higher rate (above about 60 rads/h). Conversely, at 175 rads total dose, the incidence of vomiting would increase from 10 percent to between 40 and 50 percent if the dose rate were increased from a low of 3 to 3.5 rads/h to over 60 rads/h. It can be inferred that the difference in response is due to a dose-rate modifying effect. That effect is one of the few that have been directly observed in man [Cronkite, Bond, and Dunham, 1956; and Edsall and Pemberton, 1970]. The modifying effect, though, could have been partially due to other factors such as sensitivity differences in the population sample, error in dose assessment, etc.

Another dose-rate modifying effect for the prodromal response is illustrated by the clinical assessment of a 1964 accident in Mexico involving the protracted exposure of five family members to cobalt-60 gamma radiation [Martinez et al., 1964]. The least injured family member (the father), who received about 1000 rads over an exposure period of 106 days at dose rates varying from 9 to 16 rads/day (about 0.4 to 0.7 rad/h), did not exhibit gastrointestinal symptoms, although easy fatigability was noted on the 36th day. The most severely injured family member, who received an estimated minimum dose of 3000 rads, had anorexia and vomiting after an initial exposure period of 7 days at an estimated dose rate of about 300 rads/day (12.5 rads/h); those symptoms did not recur after a subsequent 17-day period of exposure at a much lower dose rate of about 25 rads/day (≈ 1 rad/h). This experience suggests that radiation exposures received in small daily doses at low rates are not as efficient in producing prodromal responses as a single, high-intensity dose or small prompt daily doses of equal size [Langham, 1967].

Based on clinical observations of radiotherapy trials involving fractional radiation exposure over 1 to 2 weeks, the Space Radiation Study Panel [Langham, 1967] developed estimates to express the reduced efficiency of low-dose-rate radiation exposure (compared to high-dose-

rate exposure) in bringing about prodromal responses. The measure, based on incidence of symptoms, is shown in Table 1. The ratio given for prodromal response is 2.5, suggesting that low-dose-rate exposure is only 1/2.5 as effective as high-dose rate exposure in producing response. To test this assertion, clinical data from 103 patients were analyzed by Lushbaugh et al. [1968]. Table 2 summarizes the results of that analysis, and, by comparison, indicates that the occurrence of vomiting was reduced by approximately the level predicted by the National Association of Sciences/National Research Council Space Radiation Study Panel [Langham, 1967].

Figure 2 shows a plot of the incidence probability densities of the prodromal symptoms, as constructed by Lushbaugh et al. [1968]. It reveals a shift in reduced radiosensitivity when exposures are fractionated over 8 days instead of being given in a single exposure over one day. Although less pronounced for the milder symptoms (anorexia and nausea), the larger change in the dose-response relationship for vomiting lends support to the concept that prodromal response in humans decreases with lower dose rates or when the total dose is fractionated over a number of small doses. Furthermore, it provides evidence of the presence of radiation damage repair and/or "clearing mechanisms" in the human physiological system, and illustrates that, given appropriate clinical data, biological recovery can be quantified (in a gross sense).

Some further observations [Ricks et al., 1972] regarding prodromal responses (based on clinical experience of 1085 patients receiving low dose rates of less than ≈ 1 R/h) are summarized as follows:

Prodromal Response	Dose-Rate Range
Physiologically symptomless	5 to 6 R/day (0.21 to 0.25 R/h)
Nausea infrequently after 30 days or more	10 to 20 R/day (0.42 to 0.83 R/h)
No prodromal effects for 30 days or more (emesis noted after that period)	20 to 30 R/day (0.83 to 1.25 R/h)

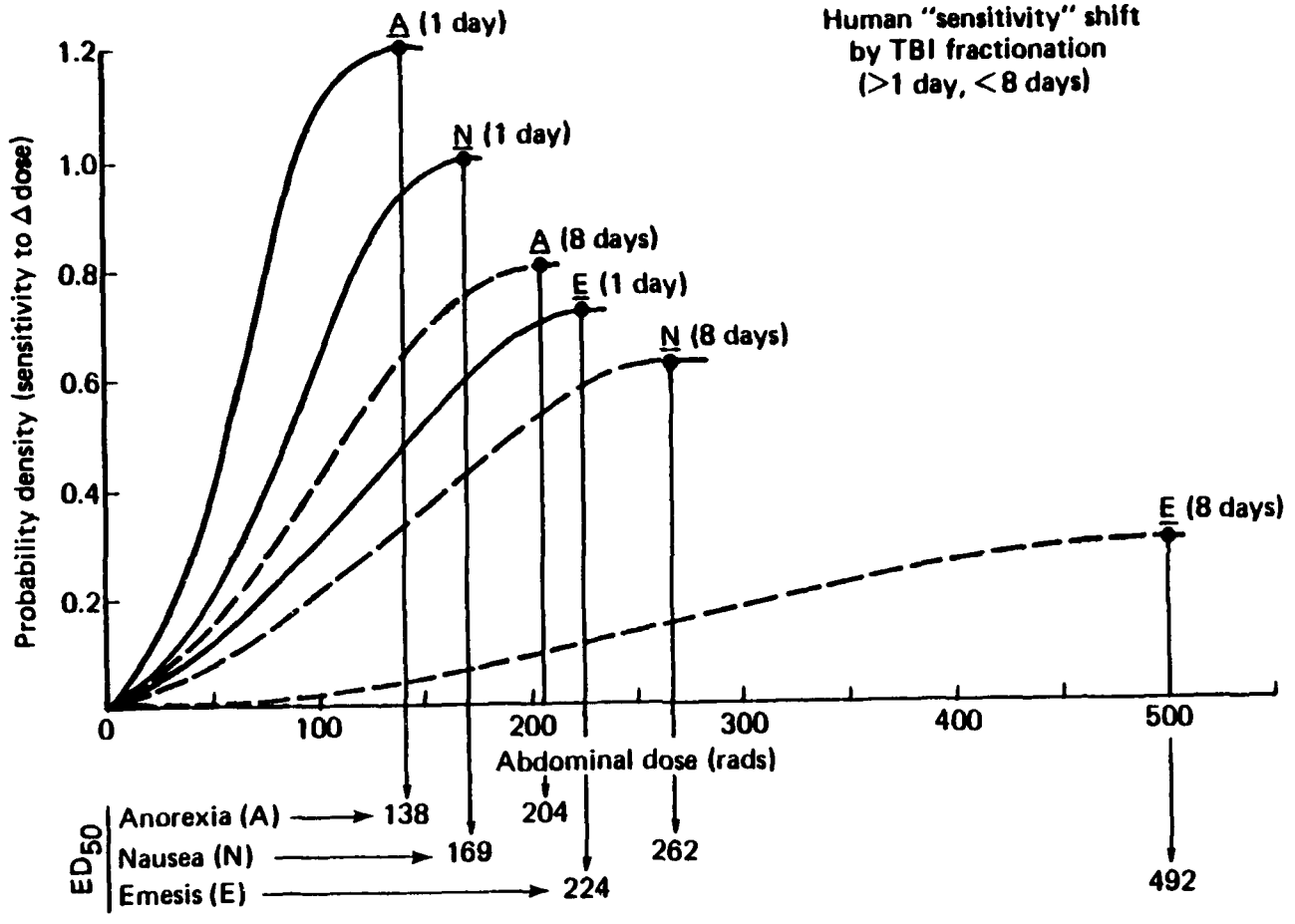
Table 1. Suggested dose-rate or rate-effectiveness factors for early responses following exposure to low linear-energy-transfer (LET) radiation.

	Duration of Exposure Needed to Produce Equivalent Responses		
	Erythema and Skin Esquamation	Prodromal Signs	Hematological Depression and Lethality
Duration of exposure at high dose rate for maximum effectiveness (A)	1-2 h or less	2-4 h or less	1-2 days or less
Duration of exposure at low dose rate for minimum effectiveness (B)	4-6 days or longer	2-4 days or longer	3-4 weeks
Ratio of dose (B/A) needed to produce equivalent response	3	2.5	2
Rate-effectiveness factor	1/3	1/2.5	1/2

Source: Langham [1967].

Table 2. Estimates of rate-effectiveness factor (f_r) for early response.

Source	f_r
Langham [1967] (normal man)	
Prodromal signs	1/2.5
Lushbaugh et al. [1968] (patient)	
Anorexia	1/1.5
Nausea	1/1.6
Emesis	1/2.2



Source: Lushbaugh et al. [1968].

Figure 2. Dose increase required to produce same incidence of prodromal symptoms if dose is fractionated over 8 days rather than 1 day.

Finally, fatigue symptoms, or, more specifically fatigability, are obviously of interest for military operations considerations. Using bicycle ergonometry [Ricks et al., 1972], decreased performance capability (based on pulmonary efficiency measurements) was observed after protracted radiation exposure at low-dose-rate regimens: (1) continuous exposure at 30 R/day (1.25 R/h) over 5 days (150 R total), and (2) after prolonged fractionated responses to 10 R daily, given at a rate of 1.5 R/h. Even though fatigability has been demonstrated at these low-dose-rate exposures, little is actually known about the quantitative aspects, such as dose/dose rates required and response time dynamics.

SECTION 3
INJURY AND RECOVERY IN ANIMALS

In this section, we review and summarize information on protracted radiation effects in animals. The data are from investigations employing various dose rates and dose levels. A number of experiments with large animals have demonstrated that the $LD_{50/30}$ (or $LD_{50/60}$)* differs significantly from that of small animals [Ainsworth et al., 1968; Bateman, Bond, and Robertson, 1962; Hanks et al., 1966a; Holloway et al., 1966; Krebs and Brauer, 1964; and Still et al., 1969a]. The values determined for large animals were shown to approach the $LD_{50/60}$ values estimated for humans. Experiments were conducted with rodents, dogs, sheep, swine, and burros to obtain data on the effect of radiation dose rate on injury, recovery, and lethality [Ainsworth et al., 1968; Baum and Kimeldorf, 1957; Page, Ainsworth, and Leong, 1968; Still et al., 1969a; Brown, Gramly, and Cross, 1964; Hanks et al., 1966a; Mobley, Godden, and deBoer, 1966; and Rust et al., 1954]. It was expected that those data would permit some cautious extrapolation to the case of humans exposed to radiation under similar conditions.

DOSE-RATE EFFECT.

The most frequently used, direct means of evaluating dose-rate effects involves determining the LD_{50} at various exposure rates [Bateman, Bond, and Robertson, 1962; Kallman, 1958; Krebs and Brauer, 1964; Krebs and Leong, 1968; Stanley, Seigneur, and Strike, 1966; Stearner and Tyler, 1963; Thompson and Tourtellotte, 1953; Traynor, Still, and Siegal, 1967; and Woodward et al., 1967].

The plot and data points in Fig. 3 are drawn from a variety of sources. The LD_{50} in sheep versus exposure rate (in roentgens per

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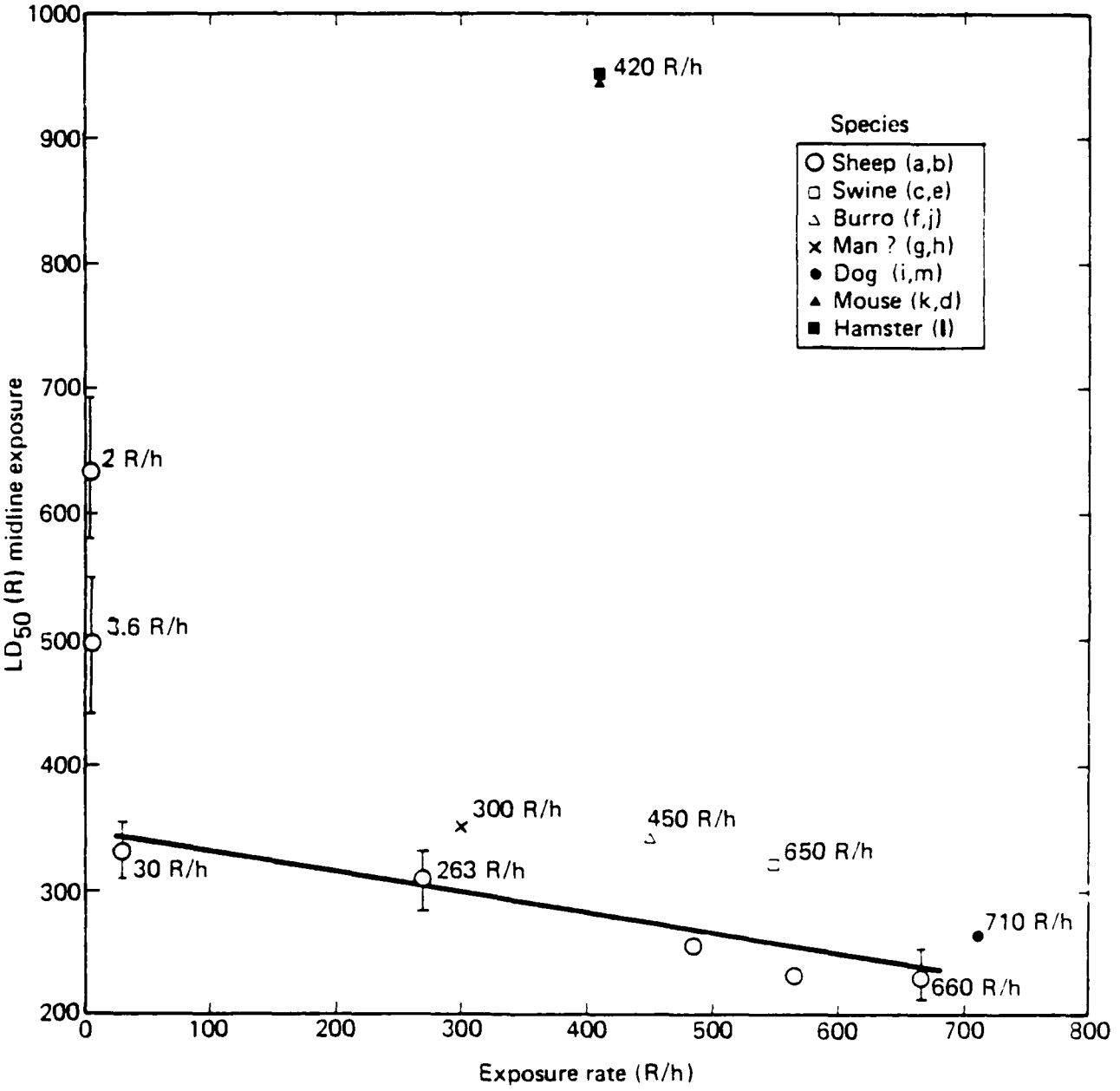
*$LD_{50/30}$ refers to the dose level of 50 percent expected lethality for most animal species within a period of 30 days postexposure; for humans and sheep $LD_{50/60}$ has the same meaning, although the postexposure observation period is 60 days rather than 30 days.



Source: (a) Hanks et al. [1966a]; (b) Page, Ainsworth, and Leong [1968];
(c) Ainsworth et ai. [1968]; (d) Bateman, Bond, and Robertson [1962];
(e) Page et al. [1965]; (f) Still et al. [1969a]; (g) Cronkite and Bond [1960];
(h) Storer [1964]; (i) Alpen and Baum [1964]; (j) Brown and Cragle [1968];
(k) Leong, Wisecup, and Grisham [1964]; (l) Holloway et al. [1966];
(m) Bond et al. [1956].

Figure 3. Relationship of LD_{50} to exposure rate for mammals.

hour) is shown as a straight line. The plot shows that the LD_{50} decreases as the exposure rate increases, until the rate reaches approximately 700 R/h. In addition, the LD_{50} for specific dose rates is shown for dogs, swine, and burros. Also shown is an estimate for humans. From the plot, it is concluded that sheep may be somewhat more radiosensitive than the other species, although, in general, all the larger animals respond similarly to radiation injury. Clearly, sheep are a factor of 3 more sensitive than small animals (represented by the mouse and the hamster). The LD_{50} for those animals is approximately 940 R at a dose rate of 420 R/h.

Although it has been shown that the LD_{50} decreases as the exposure rate increases in large animals [Ainsworth et al., 1968; and Page, Ainsworth, and Leong, 1968] and small ones [Bateman, Bond, and Robertson, 1962; and Krebs and Brauer, 1964], experimental evidence indicates that a dose-rate limit is reached beyond which no further modifying effects are noted (i.e., the curve approaches a constant value). In a study to evaluate the effects of combined neutron and gamma dose rate on lethality in dogs, it was observed that the LD_{50} differed only by 9 rads, i.e., 230 and 221 rads, in animals exposed to 2400 rads/h and 3.6×10^7 rads/h, respectively [Ainsworth et al., 1964; Ainsworth et al., 1965; and Spalding, Sayeg, and Johnson, 1964].

Other experimental studies with large animals also indicate that sheep appear to be the most radiosensitive. Table 3 compares LD_{50} results from studies performed with sheep [Hanks et al., 1966a] to those with swine [Ainsworth et al., 1968; Nachtwey, Ainsworth, and Leong, 1967] at high dose rates (450 and 480 R/h).

Mortality studies were also conducted on sheep [Page et al., 1971] and swine [Ainsworth et al., 1968; and Nachtwey, Ainsworth, and Leong, 1967], at low dose rates of 3.6 and 4.0 R/h, respectively. For swine, no mortality was observed for doses up to 1550 R; the investigators estimated that the lethal range for swine at 4.0 R/h would be between 2000 and 2400 R. The data from these studies indicate that for the low dose rates used, swine are more radioresistant than sheep. Exposure of sheep up to 400 R at a dose rate of 3.6 R/h resulted in residual injury that amounted to 85 percent of the LD_{50},

Table 3. LD_{50} for sheep and swine (in roentgens).

	550 R/h Co^{60} γ-rays	480 R/h X-rays
Sheep[a]	237 (215 to 257)	252 (233 to 276)
Swine	333 (286 to 374)[b]	399 (371 to 424)[c]

[a]Hanks et al. [1966a].
[b]Ainsworth et al. [1968].
[c]Nachtwey, Ainsworth, and Leong [1967].

whereas the residual injury in swine exposed to somewhat higher levels (500 R at 4 R/h) amounted to only 36 percent of the LD_{50}.

LOW-DOSE-RATE EXPOSURE--INJURY AND RECOVERY IN SHEEP.

The effect of low dose rates on injury and recovery was determined from sheep irradiation studies by Hanks et al. [1966a, 1966b]. The "split-dose technique" was employed--groups of sheep were first exposed to a dose of 165 R at dose rates of 0.5, 0.95, 1.85, and 3.9 R/h (shown in Table 4). The animals were then removed from the radiation field and their acute LD_{50} was determined within a few hours after the protracted exposure. The LD_{50} levels were compared to the LD_{50} for a single acute exposure of 237 R obtained using a high dose rate of 660 R/h. The results, given in Table 4, indicate that when sheep received a protracted exposure of 165 R at either 0.5 or 0.95 R/h, the LD_{50} levels determined afterward did not differ significantly from those of normal controls. The negative values of residual injury in Table 4 indicate the possibility of a small "over-recovery." However, when the exposure rate was increased to 1.85 and 3.9 R/h, the LD_{50} quantities were significantly lower than the control LD_{50}.

The results indicate that all injury sustained by an animal during irradiation is repaired when the dose rates are less than about

Table 4. Injury repaired for 165 R exposure protracted at various dose rates.

	Dose Rate (R/h)[a]			
	0.50	0.95	1.85	3.90
$LD_{50/60}$[b]	268(224 to 328)	279(244 to 323)	162(141 to 182)	133(106 to 162)
Residual injury at completion of protracted exposure (roentgens)[c]	-31	-42	75	104
Roentgens repaired (roentgens)[d]	196	207	90	61
Duration of protracted exposure (hours)	340	180	89	42
Roentgens repaired/hour	0.58	1.15	1.01	1.45

[a]Midline air dose rate.
[b]Determined within hours after protracted exposure.
[c]Calculated by subtracting $LD_{50/60}$ determined at completion of protracted exposure from single acute exposure $LD_{50/60}$ of 237 R.
[d]Total exposure minus acute $LD_{50/60}$ (273 R).
Source: Hanks et al. [1966a, 1966b].

1 R/h, given a total exposure of 165 R; when the dose rates are greater than 1 R/h, there is a net accumulated injury.

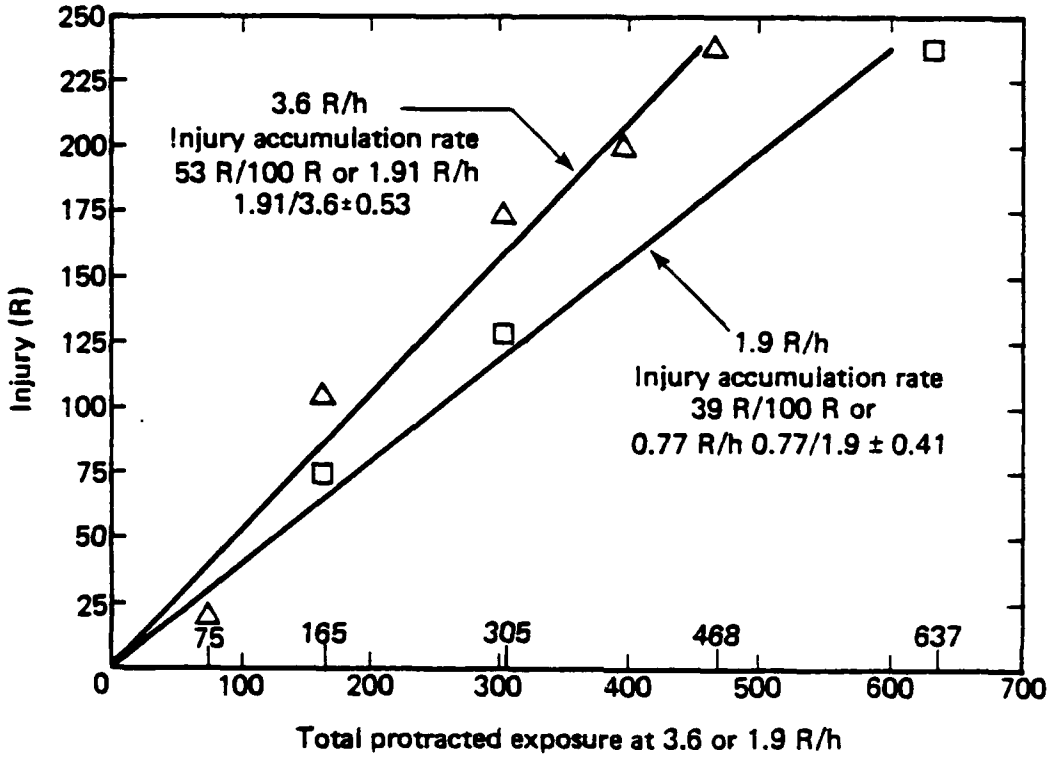
There is a limit, apparently depending on total dose, to how long sheep can continue to repair injury during radiation exposure at a rate of 1 R/h. Sheep exposed at that dose rate for 30 days were given graded exposures to determine the LD_{50} [Taylor et al., 1969]. The data indicate the LD_{50} is below 100 R. Therefore, the animals probably accumulated an estimated 140 to 180 R of net injury during the period of protracted exposure. It can be conjectured that injury accumulation occurred during the latter part of the period, but that must be experimentally verified. However, these results do indicate that animals have a finite capacity for recovery from radiation injury that decreases with the accumulation of dose.

Injury accumulation at dose rates of 1.9 and 3.9 R/h in sheep was determined from additional irradiation experiments [Ainsworth et al., 1968]. The results, summarized in Fig. 4, show injury accumulates at a rate of 53 R per 100 R for an exposure rate of 3.6 R/h and 39 R per 100 R for an exposure rate of 1.9 R/h; this amounts to a net injury increase of about 36 percent for a dose rate increase of about 89 percent. Since injury at 3.6 R/h accumulates at 53 R/100 R, the recovery in sheep amounts to 47 R per 100 R of exposure; at the 1.9 R/h dose rate, recovery amounts to 61 R/100 R.

POSTIRRADIATION RECOVERY TIME PROFILE.

Irradiation experiments were performed on sheep to determine the postirradiation recovery after cessation of both acute and protracted exposures [Page et al., 1971; and Taylor et al., 1969]. The LD_{50} values given in Fig. 5 were determined for specific times after initial conditioning exposures. The acute conditioning doses were either 165 R cobalt-60 γ-rays (given at 660 R/h) or 177 R X-rays (given at 450 R/h); protracted exposures were given at dose rates of 1.9 or 3.9 R/h cobalt-60 γ-rays. The LD_{50} values for controls were 252 R for 1 MVp X-rays and 237 R for cobalt-60 γ-rays.

When no time is allowed for recovery, the LD_{50} for sheep conditioned with acute X-ray exposure is the difference between the control



Source: Ainsworth et al. [1968].

Figure 4. Injury accumulation in sheep exposed at 3.6 or 1.9 R/h.

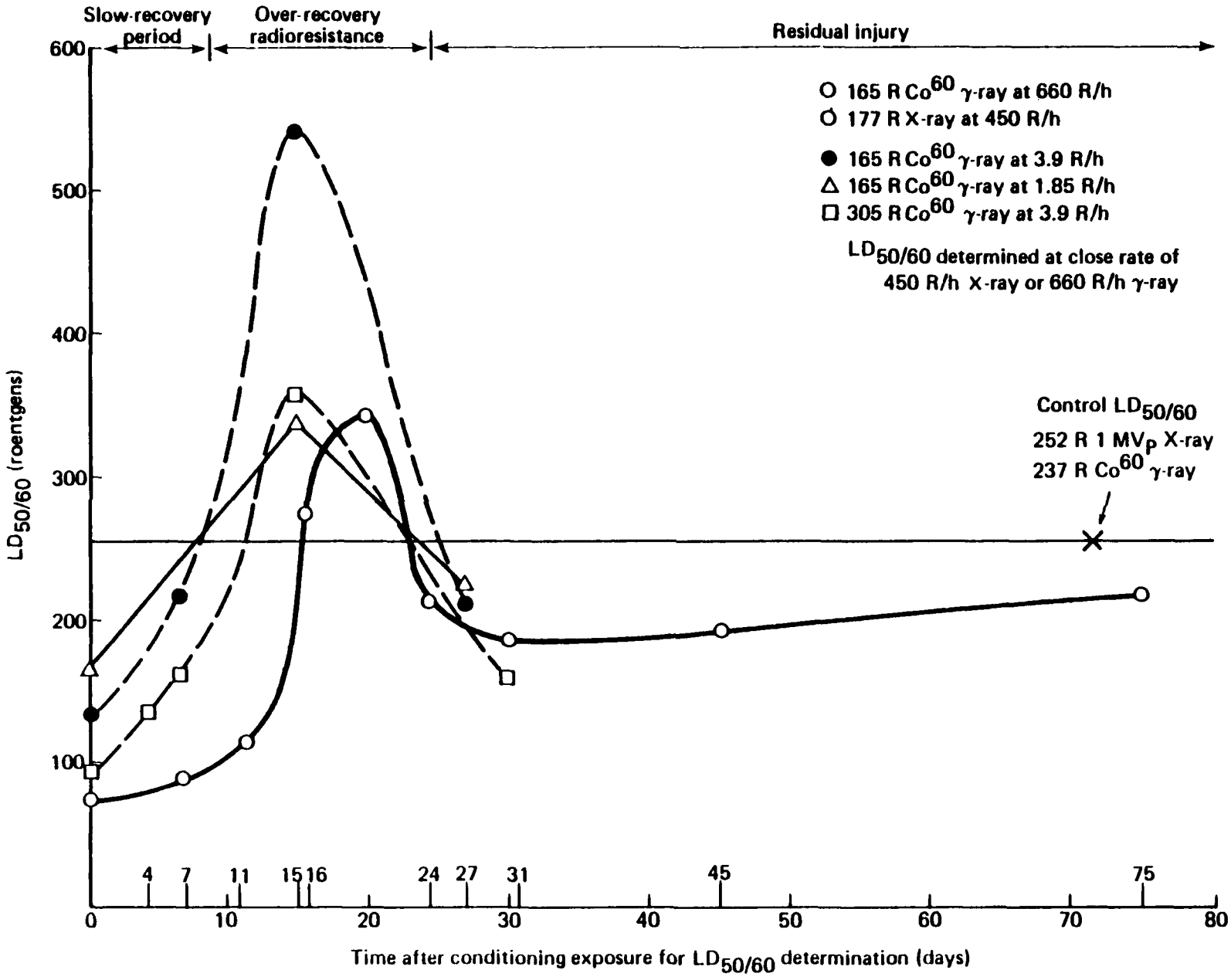


Figure 5. Recovery of sheep, as measured by $LD_{50/60}$, after irradiation at various dose rates.

LD_{50} of 252 R and the acute conditioning dose of 177 R, which is 75 R (ordinate value in Fig. 5). Although the curve drawn through the open circles for acute conditioning exposure (450 and 660 R/h) suggests a slight increase in LD_{50} between 7 and 11 days, the investigators did not consider it significant at the 95-percent confidence level. However, between days 11 and 16 significant recovery takes place; it peaks around the 20th day, when recovery apparently exceeds the acute LD_{50} control value by about 90 R. This increased resistance observed on the 20th day represents an "over-recovery" of about 37 percent or about 137 percent recovery from the conditioning exposure. By day 24, the animals return to a more radiosensitive state, reaching a nadir at day 31, which persists until at least day 75. Between days 31 and 75 the residual injury component ranges from about 29 to 16 percent, respectively. Sheep subjected to an acute conditioning dose, therefore, have an initial phase of slow recovery, followed by rapid changes in radiosensitivity including transient radioresistance, and finally, a rather long period of residual injury [Page et al., 1971].

Protracted radiation conditioning exposure created cyclic recovery patterns, similar to those noted after acute radiation conditioning; however, significant differences are seen in the recovery profile time-phasing as indicated in Fig. 5. Judging from the 5-day difference between the acute and protracted exposure peaks, sheep exposed to protracted conditioning dose appear to recover sooner than those exposed to acute radiation doses. Also, sheep exposed to a lower total conditioning dose appear to recover earlier than those given a higher dose, as indicated by the somewhat larger LD_{50} values at zero time. The zero point in Fig. 5 represents the time at which the conditioning doses were terminated. The low-dose-rate exposures (1.85 and 3.9 R/h) were given over a period ranging from about 1.8 to 3.7 days prior to the zero point and appreciable recovery had already taken place. In contrast, the acute radiation conditioning period lasted only 15 to 24 min. In general, it appears that recovery in sheep occurs earlier if the exposure is protracted rather than acute, and if the conditioning dose is low. To develop this conclusion more thoroughly, additional experimental work is necessary.

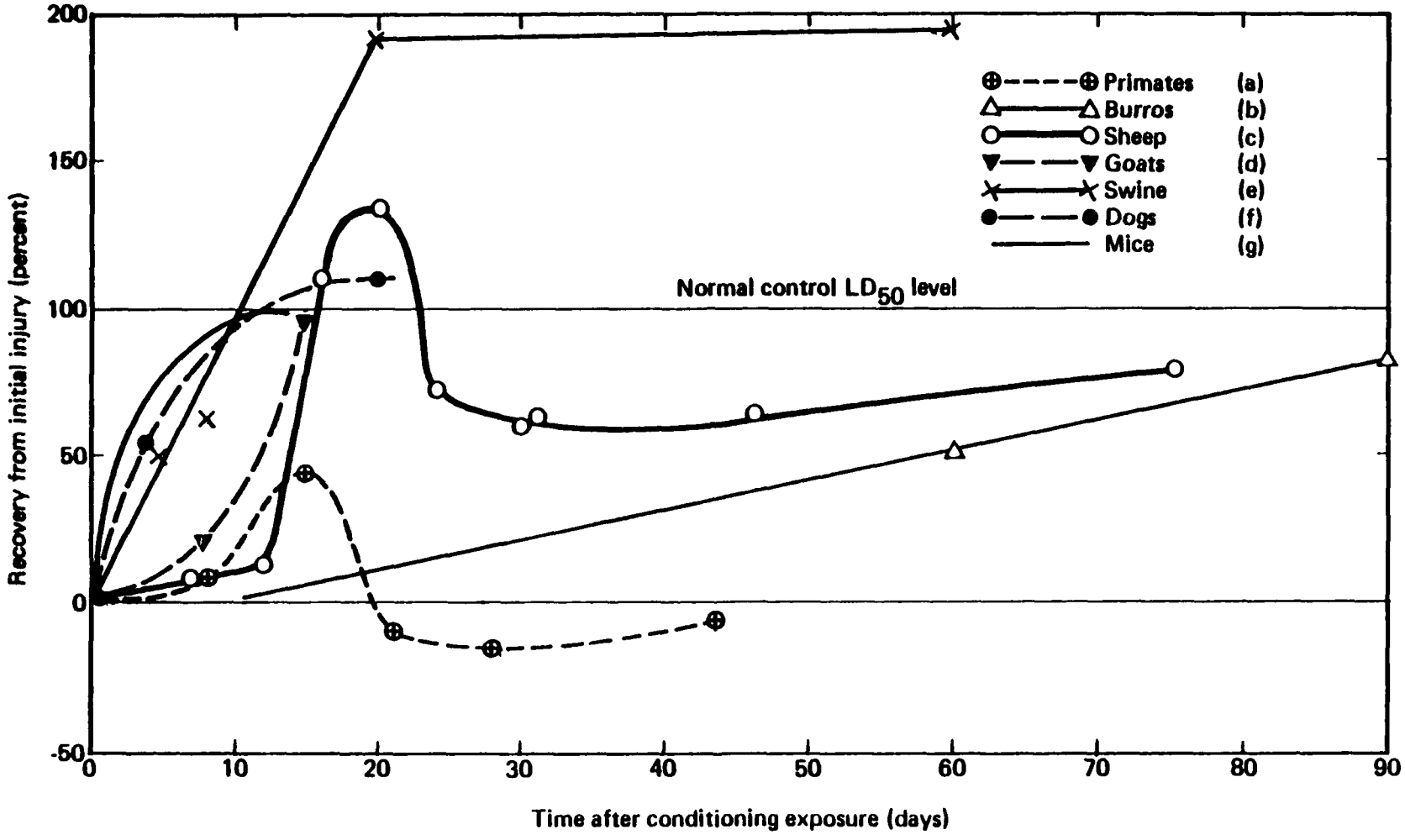
Drawing from the work of various investigators, we can compare recovery times for sheep exposed to acute radiation to recovery times for other mammals [Ainsworth and Leong, 1966; Bond, Fliedner, and Archambeau, 1966; Brown and Cragle, 1968; Eltringham, 1967; Michaelson, Orland, and Howland, 1962; Nachtwey, Ainsworth, and Leong, 1967; Page, Ainsworth, and Leong, 1968; Spalding, Trujillo, and LeStourgeon, 1961; Still et al., 1969a, 1969b; Storer, 1961, 1964; Taylor et al., 1971; Mobley, Godden, and deBoer, 1966; Page et al., 1965; and Rust et al., 1954]. Again, the method used to determine recovery from acute radiation injury was the split-dose technique, which essentially constitutes determinations of the change in LD_{50} with time after sublethal radiation injury. The results of several studies using that technique are depicted in Fig. 6.

The recovery curves in Fig. 6 were obtained from different animals under similar experimental conditions. All the animals were bilaterally exposed to 1 MVp or 250 KVp X-rays, except for the rhesus monkeys, which were exposed to cobalt-60 γ-rays by the rotating method. The conditioning dose in all cases was approximately two-thirds of the acute LD_{50}.

As shown in Fig. 6, the recovery for larger animals (sheep, goats, and burros) is delayed compared to smaller ones (mice, swine, and dogs). Partial recovery, then a reversal, occurs in primates [Ainsworth et al., 1968; Allen et al., 1960; and Eltringham, 1967]. Resistance, or over-recovery, resulting in an LD_{50} greater than the expected normal value occurs with sheep, swine, and dogs. Resistance in swine appears to be long lasting [Nachtwey, Ainsworth, and Leong, 1967]. The burro and primate show extremely slow recovery [Page, 1968]. It is apparent from Fig. 6 that no simple relationship adequately describes the recovery kinetics for all species.

INITIAL ACUTE EXPOSURE AND SUBSEQUENT LOW-DOSE-RATE RECOVERY.

The effect that an initial, acute (high dose rate) dose has on the biological recovery for a subsequent period of low-dose-rate exposure is illustrated by two specific sheep irradiation studies. First, Still et al. [1969c] measured a single acute exposure LD_{50} of



Source: (a) Eltringham [1967]; (b) Still et al. [1969a]; (c) Page, Ainsworth, and Leong [1968]; (d) Taylor et al. [1971]; (e) Nachtwey, Ainsworth, and Leong [1967]; (f) Ainsworth and Leong [1966]; (g) Blair [1963].

Figure 6. Kinetics of recovery following sublethal exposure of approximately 2/3 rads of acute (high dose rate) LD_{50}.

314 R for sheep exposed to 2 MVp X-rays at a dose rate of 450 R/h. They also exposed sheep to an acute dose of 155 R at a dose rate of 510 R/h followed by a low dose rate of 3.9 R/h until lethality occurred. The LD_{50} determined under this regimen was 326 R, which did not differ significantly from the single acute exposure LD_{50}, i.e., 314 R. Also, in view of the fact that the LD_{50} reported by Page, Ainsworth, and Leong [1968] was 495 R based on a dose rate of 3.6 R/h, Still and his coauthors concluded that the initial acute exposure (155 R at 510 R/h) had effectively prevented recovery during the subsequent low-dose-rate exposure period. Since the residual injury for the acute exposure was 314 - 155 = 159 R; whereas, that for the protracted exposure was 326 - 155 = 171 R, Still et al. estimated the increase of recovery to be only 171 - 159 = 12 R or (12/159) × 100 = 7.6 percent. This amount may be compared to about 37 percent recovery [(61/165) × 100] after a total exposure of 165 R given at a dose rate of 3.9 R/h, with no prior acute exposure, as reported by Hanks et al. [1966b] and shown in Table 4.

In a subsequent study by *Jones and* Krebs [1970, 1971], sheep were given initial doses of 9.1 or 45 R (both at a higher dose rate of 575 R/h) followed immediately by exposure to 134 R (at a lower dose rate of 3.8 R/h). Those were followed immediately by the remainder of the total dose-to-lethality, given at the initial higher dose rate (575 R/h). Their research showed that recovery was only 12 percent for the case of 9.1 R initial acute dose given at 575 R/h, and 9 percent for the initial dose of 45 R at 575 R/h. Those results are consistent with the trend of a decrease in recovery during the low-dose-rate exposure period when the initial dose rate is much higher. Recovery is slightly greater if the initial dose, at the higher dose rate, is smaller.

SUMMARY.

The human $LD_{50/60}$ response to protracted radiation exposure is thought to be similar to that in larger animals and significantly different from that in smaller ones. Of the larger animals, swine show the most pronounced recovery from protracted radiation injury.

The LD_{50} for sheep (and probably for other larger animals as well) decreases linearly with exposure rates from about 30 to 700 R/h; from 700 to 2400 R/h, a limit is reached beyond which the LD_{50} becomes constant (i.e., no further recovery is observed). A pronounced increase in LD_{50} is observed beginning with dose rates of less than about 30 R/h. At dose rates of 0.5 and 0.95 R/h, and at least up to total doses of 165 R, complete recovery occurs in sheep during exposures. When the dose rate is increased to 1.85 and 3.9 R/h, residual injuries of 75 or 104 R, respectively, occur. However, a continuous dose rate of about 1 R/h for an extended period of 30 days results in an injury accumulation rate between 0.19 to 0.25 R/h. Injury accumulates more rapidly in sheep at 3.6 R/h than at 1.9 R/h, given the same total dose.

Postirradiation recovery oscillates. In sheep, slow recovery up to about day 7 is followed by rapid recovery until about day 20. Beyond that and for a period of at least 75 days, residual injury is measured. Recovery in larger animals is not uniform in either magnitude or postirradiation time. Recovery may be earlier in smaller animals than in larger ones, and only partial in primates. Sheep exposed to protracted doses appear to recover faster than those exposed to acute doses. The biological recovery capability of animals at low dose rates (3.8 R/h) decreases with the magnitude of an initial acute dose. This decreased recovery capability has been demonstrated in sheep for initial acute doses at higher dose rates (9.1 and 45 R at 575 R/h, and 155 R at 510 R/h).

SECTION 4
INJURY ACCUMULATION MODELS

Modeling that has been performed and which takes into account the biological recovery and repair of radiation injury in complex organisms is primarily based on research with animals ranging in size from the mouse to the burro [Bond, Fliedner, and Archambeau, 1966; and Still et al., 1969b]. Limited data have also been derived from cancer patients undergoing radiotherapy and from radiation accident victims. Modeling of that kind would be expected to show general trends, but otherwise would be quite diverse due to the varied nature of data sources. In this section, models and guidelines for protracted radiation exposure that have appeared in various publications are reviewed and compared.

Modeling has been developed for cell or specific tissue-level response, as well as for the whole organism. Various medical applications that make use of ionizing radiation have contributed to the research in the areas of cell- and tissue-level repair. Marked advances in radiotherapeutic techniques, which have led to greater success in the use of ionizing radiation in treating cancer patients, can be largely attributed to radiobiological research involving cell- and tissue-level repair and modeling studies. In that field, there is a high degree of focused consensus among experts.

However, when the organism as a whole is considered, the state of affairs involving knowledge of biological repair is quite different. There are three basic reasons for that. First, unlike studies performed on laboratory animals, isolated cell and tissue studies offer the convenience of experimental control and greater assay precision. Second, since radiotherapeutic techniques largely focus on the treatment of specific tissue masses (tumors) and cell types, cell- and tissue-level research can be more directly related to clinical application. Third, the complexity of the organism as a whole presents a formidable problem for any collective-response interpretation, if approached mechanistically from the cell and tissue level.

Naturally then, research on biological repair of ionizing radiation damage in complex organisms has been sparse over the last ten years, resulting in a dearth of published information on the subject. Consequently, there is no high degree of focused consensus among radiobiological experts when it comes to biological repair modeling of the organism as a whole.

Because lethality (specifically, 50 percent lethality) represents an unambiguous response observed by the researcher, it is the endpoint most frequently chosen for animal studies involving sensitivity to ionizing radiation, as well as body recovery. To illustrate biological recovery based on selected models, we also employ the lethality endpoint in terms of the LD_{50} versus exposure dose rate. However, that raises the question of the validity of globally applying those models to military operations planning for all manner of recovery from radiation injury. In that context, two basic issues come to mind.

First, the biological recovery process (perceived to more efficiently reduce radiation damage when exposure is protracted) is probably quite different for initial response endpoints such as nausea, vomiting, and fatigue, than it is for the lethality endpoint. However, we assume that the two endpoints operate under the same principle of reduced effect (or a larger total dose requirement). In fact, the recovery process for an initial response may be more like a "detoxification action" than "biological recovery" per se, and would likely require a different modeling approach, particularly for short time periods.

Second, LD_{50} should be a useful indication of biological recovery for the purposes at hand. For the purpose of military planning, in which the minimum objective is to maintain dosages below a certain level (i.e., lethality) or to minimize such exposures, then it is clearly of interest to know the conditions under which exposure would be lethal. There is reason to believe that the recovery process is not less effective but possibly more effective, in the sublethal dose range than in the lethal range. Therefore, errors may be introduced by applying biological recovery rates inferred from high lethal

exposures to situations of lower intensity, sublethal exposure. Those errors would tend to overestimate the net injury for protracted exposure.

In the model descriptions below, we perform some algebraic manipulation in order to provide a common basis for comparison. This involves expressing the independent variable in terms of average dose rate. Dose units chosen to illustrate the models are tissue rads--bone marrow or midline body dose (for purposes here, we do not distinguish between the two and use the conversion, rads = 0.66 R). Also, where possible, values for parameters and boundary conditions are those suggested in published sources, although in some cases we chose a common normalizing value of 300 rads for the high dose rate ($\geq$ 600 rads/h) or prompt LD_{50}.

MODELS.

The models discussed here are all represented in plot form in Fig. 7, although they are addressed individually in the text.

Strandqvist.

The Strandqvist power function model [Strandqvist, 1944] has the form

$$D = D_0(t/168)^b \quad \text{(rads)} , \quad t \geq 168 \text{ h (1 wk)} , \tag{1}$$

where D_0 is the assumed nominal single lethal dose in rads (midline absorbed photon energy) for an exposure protracted over one week, t is the time for exposures beyond one week, and b is the exponent of t or the slope constant of the log-log regression used to obtain a best fit of clinical data as pointed out by Lushbaugh [1982]. In order to express dose D as a function of a constant dose rate r (rads/h), substitute t = D/r in Eq. (1) and obtain

$$D = D_0^{[1/(1-b)]} \cdot (168/r)^{-[b/(1-b)]} \quad \text{(rads)} . \tag{2}$$

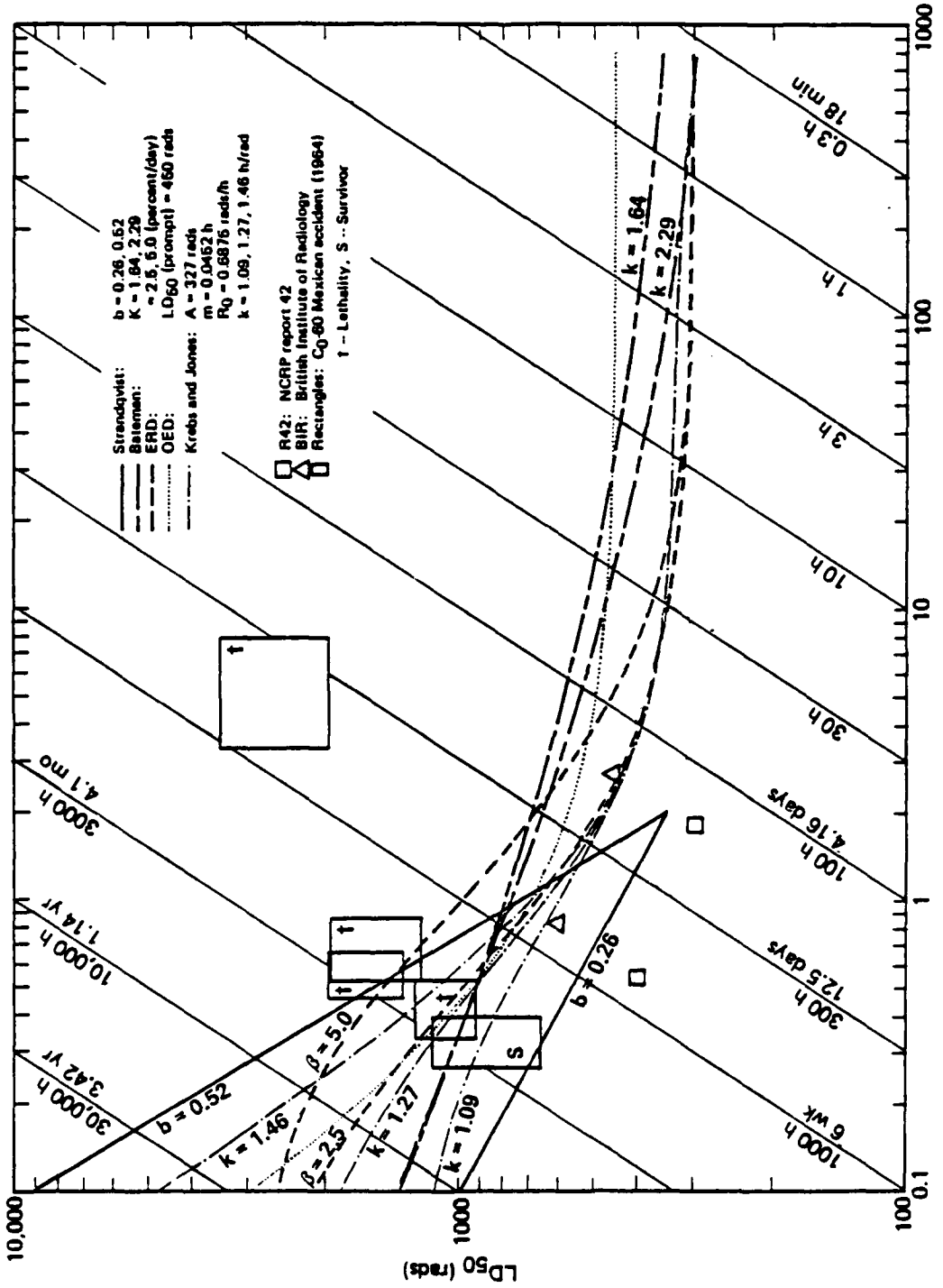


Figure 7. Protracted dose-rate models.

Using values for D_0 and b given in Lushbaugh [1982] as 345 rads and 0.26, respectively, gives the following relationship, that is plotted in Fig. 7:

$$D = 345^{1.351} \cdot (168\ r)^{-0.351} \quad \text{(rads)} . \tag{3}$$

Also, a study of clinical and accident data indicated that the slope may be increased by as much as two or three times if the exposed persons have normal, healthy hematopoietic systems [Yuhas, Stokes, and Lushbaugh, 1972]. For the purpose of illustration, the following relationship is also plotted in Fig. 7. It reflects doubling the slope, i.e., b = 0.52.

$$D = 345^{2.083} \cdot (168\ r)^{-1.038} \quad \text{(rads)} . \tag{4}$$

Bateman.

Bateman [1968] showed that dose-rate effects follow a linear function of the reciprocal cube root of dose rate. That finding was based on data for such endpoint effects as human dermal responses and lethality of mice, rats, swine, and sheep. This relationship takes the form

$$D = D_0 \left(1 + \frac{K}{r^{1/3}}\right) \quad \text{(rads)} , \tag{5}$$

where D_0 is the single dose requirement for rapid (or prompt) exposure, D is the isoeffective dose at a much lesser dose rate r and K is a constant related to the recovery kinetics of the animal species and the cellular systems involved.

The Bateman model plotted in Fig. 7 is illustrated by two different curves based on two different approaches in selecting values for D_0 and K, although both utilize dose and dose-rate estimates based on the 1964 Mexican accident involving cobalt-60 γ-ray exposure [Martinez et al., 1964]. In that accident, five family members were

exposed to varying levels of radiation for periods of time ranging from an estimated 24 to 115 days; only one family member (father) survived.

There is considerable uncertainty in the actual dose and dose rate values received by the accident victims as indicated by the "rectangles" in Fig. 7, and it is difficult to ascertain an LD_{50} value with any reasonable degree of confidence by applying standard statistical techniques. Rather, as indicated below, we have estimated an LD_{50} value and corresponding dose rate based upon averaging the midpoint values from the dosage ranges given for the survivor (father) and nonsurviving family member with closest corresponding exposure (daughter).

	LD_{50} (rads)	Dose Rate (rads/h)
Nonsurvivor (daughter)	(906-1236) 1071	(0.33-0.53) 0.43
Survivor (father)	(649-1133) 891	(0.26-0.40) 0.33
Average	891	0.38

One approach in plotting the Bateman model in Fig. 7 fixes a value of D_0 = 300 rads for the prompt dose and anchors the low dose rate and corresponding accumulated LD_{50} according to the averaged values obtained above from the Mexican accident. That yields a value of $K = 1.64$ (rads/h)$^{1/3}$. The other approach also anchors the Bateman relationship according to the Mexican accident and in addition, we set LD_{50} = 300 rads at a dose rate of 600 rads/h. This yields values of D_0 = 236 rads and $K = 2.29$ (rads/h)$^{1/3}$.

Krebs and Jones.

Based on their work in irradiating sheep with cobalt-60 γ-rays, plus a comprehensive review of previous animal irradiation studies involving mice, dogs, swine, sheep, and goats, Krebs and Jones [1975] formulated protracted dose response relationships for biological repair for dose rates ranging from about 0.4 to several hundred roentgens per hour using LD_{50} as the endpoint. This represents the

range over which the LD_{50} is dependent upon dose rate. Based on data from dog, pig, and mouse irradiation studies, Krebs and Jones further indicate that lethal dose becomes dependent upon dose rate when the time required to deliver it is longer than about 30 min (our illustration of their model also presumes that to be the case). Also, our discussion of their model below is given in terms of roentgen (R) units in keeping with their reporting, although for the plot illustration we convert to dose units of rads midline body or bone marrow tissue.

The model suggested by Krebs and Jones includes a linear relationship of LD_{50} as a function of dose rate r (in roentgens per hour) for high dose rates, combined with an exponential repair relationship for low dose rates. The linear relationship is of the form

$$LD_{50} = A - mr \quad (R) , \tag{6}$$

which expresses an increase in LD_{50} for a decreasing dose rate in the range between 600 or 700 R/h down to about 30 R/h. The intercept and slope parameters A and m vary depending upon animal species. As mentioned above, Krebs and Jones indicate that when lethal exposures are received over a period of about 30 min or less, the corresponding LD_{50} versus dose-rate relationship flattens. Accordingly, to illustrate their model here, the LD_{50} value for dose rates in excess of 600 to 700 R/h is assumed to be flat, which corresponds to no apparent repair.

Krebs and Jones also point out that the linear form [Eq. (6)] rapidly begins to underestimate biological repair for dose rates less than about 30 R/h. Furthermore, from about 30 R/h down to about 0.4 R/h their interpretation of animal data indicates an apparent transition from a strictly linear repair relationship with dose rate to one that includes an exponential form. The authors fit an exponential repair relationship to data of the form

$$R = R_0(1 - e^{-kr}) \quad (R/day) , \tag{7}$$

where R_0 is the maximum daily repair rate, estimated to be about 25 R/day and k (in days per roentgen) is a dose repair constant. Note that this relationship indicates a progressively less efficient rate of biological repair with an increase in exposure rate, i.e., (daily repair rate)/(daily exposure rate),

$$\frac{dR}{dr} = R_0 k e^{-kr} . \tag{8}$$

From their studies, Krebs and Jones suggest a relationship for the effective LD_{50} as a function of dose-rate exposure, which is developed as follows. The net accumulated injury rate per day is

$$I_{net} = r - R \quad (R/day) . \tag{9}$$

Accordingly, the time-to-lethality T based on continuous radiation exposure is

$$T = \frac{LD_{50}}{I_{net}} \quad (day) . \tag{10}$$

The effective accumulated lethal dose LD'_{50} is then

$$LD'_{50} = rT \quad (R) . \tag{11}$$

Substituting Eqs. (6), (7), (9), and (10) and expressing exposure dose rates r in terms of rads per hour, Eq. (11) may be rewritten as

$$LD'_{50} = \frac{r(A - mr)}{r - R_0(1 - e^{-kr})} \quad (rads) . \tag{12}$$

The relationship above provides a reasonable means to estimate the protracted midlethal dose based on observations from animal irradiation studies. However, Krebs and Jones point out limitations that correspond to the maximum recovery rate R_0. Their estimates of R_0 (about 25 R/day) are based on a dose rate of about 3.8 R/h and less. For higher dose rates, they suggest scaling down that value in proportion to the linear component of the LD_{50} dose [Eq. (6)] given by $R_0(A - mr)/A$. In illustrating the model here, we have neglected to make that adjustment. Also, some of the data from animal irradiation studies appear to suggest that the recovery rate may, to some extent, depend on the rate of dose accumulation. We have not attempted to account for that.

Equation (12) above requires specifying four parameters--A, m, R_0, and k. Based on their own studies and on that of Lushbaugh et al. [1967], which were based on human therapy irradiations, Krebs and Jones suggest means of estimating the parameters for application to humans. They further point out the marked sensitivity of the effective lethal dose LD'_{50} to the k parameter. For Eq. (12), illustrated in Fig. 7, we chose A = 327 rads and m = 0.045 (h). Using Eq. (6), these values were obtained assuming an LD_{50} of 300 rads for a dose rate of 600 rads/h, and an LD_{50} of 325 rads for a dose rate of 46.6 rads/h. The latter dose rate represents an average value from therapy patients [Lushbaugh, 1967] and 325 rads is assumed to correspond to the LD_{50} for "healthy" humans. For R_0 we chose 0.69 rads/h (16.5 rads/day) and values of k = 1.09, 1.27, and 1.46 h/rad; these are within the range suggested by Krebs and Jones.

Equivalent Residual Dose.

One particular model of protracted radiation exposure effects is probably the most frequently used and primarily applied to planning and guidance for military and civil defense operations. It is based on what is referred to as the equivalent residual dose (ERD), derived from an original theory proposed by Blair [1952a, 1952b, 1953, 1954, 1956, and 1963].

The ERD model can be traced to Blair's studies of the effect of ionizing radiation exposure in shortening the life spans of the mouse, guinea pig, rat, and dog. To a first approximation, that model assumes that the recovery rate is a constant percentage of the net injury rate. Furthermore, Blair's model accounts for a part of the injury that is either permanent or occurs so slowly that it is, for all practical purposes, permanent.

Davidson [1957] used a modified form of the Blair model, together with available data on animals and humans, as the basis for a thorough operations research analysis of the effects of gamma radiation on human beings. The National Committee on Radiation Protection and Measurements (NCRP) also based guidance recommendations for radiation exposure in an emergency on a form of the Blair model [1962]; subsequent NCRP guidance [1974] which was more practical for operational conditions during and after a nuclear attack, also drew upon the Blair model, modified to consider human recovery rates. Knapp [1965] incorporated the ERD model in assessing weapon fallout radiation effects on the public and for the design of fallout shelters. Schmidt [1981] also used the ERD model in fallout pattern studies.

Stated mathematically, the ERD model is:

$$ERD = D_0 \left[f + (1 - f)e^{-\beta t} \right] \quad \text{(rads)} , \tag{13}$$

where D_0 is a dose delivered in a single short exposure, f is the irreparable fraction, and β is the repair constant, which can also be expressed as $\beta = 0.693/T_R$ (with T_R being the time required to repair one-half the reparable portion of the injury). That form can be extended to estimate the ERD for a continuous radiation exposure rate $r(\tau)$, delivered over a period of time T_e, given by the convolution integral:

$$ERD = \int_0^{T_e} r(\tau) \left[f + (1 - f)e^{-\beta(t-\tau)} \right] d\tau \quad \text{(rads)} . \tag{14}$$

Assuming a constant exposure rate over time (for convenient illustration) and integrating, yields the following:

$$ERD = r\left\{fT_e + \frac{(1-f)}{\beta}\left[e^{-\beta(t-T_e)} - e^{-\beta t}\right]\right\} \quad \text{(rads)} . \qquad (15)$$

For the purpose of comparing the various models discussed here, we assume $t = T_e$, and obtain

$$ERD = r\left[ft + \frac{(1-f)}{\beta}(1 - e^{-\beta t})\right] \quad \text{(rads)} . \qquad (16)$$

In the various ERD model application studies pointed out above, values of $f = 0.1$ (10 percent irreparable injury) and constant repair rate of 2.5 percent per day of reparable injury fraction were commonly chosen. Therefore, in order to conform with those choices the ERD model illustrated here uses $f = 0.1$ and $\beta = 0.025/24 = 0.001042\ (h^{-1})$. Also for purposes of comparison, the repair rate is doubled to 5 percent per day where $\beta = 0.002084\ (h^{-1})$.

The models illustrated in Fig. 7 are plots of lethal dose (LD_{50}) against dose (exposure rate), whereas Eq. (16) is in terms of time. Accordingly, adjustments are made in representing the ERD model for plotting LD_{50} as a function of dose rate. Assuming a value of 300 rads for the prompt LD_{50}, we set ERD = 300 rads and the accumulated dose $D = rt$. Equation (16) can then be rewritten in the form

$$D = \frac{1}{f}\left[300 - \frac{(1-f)}{\beta}(1 - e^{-\beta D/r})\right] \quad \text{(rads)} , \qquad (17)$$

which is a transcendental relationship whose solution is obtained iteratively and plotted in Fig. 7.

Operational Evaluation Dose.

The operational evaluation dose (OED) also referred to as the operational equivalent dose, is an algorithm developed in British

medical circles [British Medical Association, 1983] to provide advice regarding a radioactive fallout environment for (1) radiation protection in shelters or refuges, (2) the public or movement out of shelter, and 3) deployment of individuals carrying out essential tasks in and through high dose rate radiation areas. The OED was reviewed by a working party established by the Home Office Scientific Research and Development Branch [1985] for guidance and planning purposes. According to the British Medical Association [1983], its intended use is as a guide for casualty criteria (specifically, expected lethality levels) for radiation exposure received over periods of hours or days, rather than brief exposures received over a few minutes or less. The OED formula is

$$\text{OED} = X - 150 - 10t \quad \text{(rads, mean bone marrow)} , \tag{18}$$

where X is the accumulated dose that produces lethality (e.g., LD_{50}) for protracted exposure, and t is the number of days after the start of exposure. Equation (17) allows for recovery by the human body from a dose of 150 rads received within a short time, plus the capability of additional recovery at a rate of 10 rads per day from subsequent exposure. Since the OED in Eq. (17) corresponds to a short-time exposure LD_{50} value, the accumulated dose X that produces 50 percent lethality is

$$X = \text{OED} + 150 + 10t \quad \text{(rads)} \tag{19}$$

where OED = 450 rads bone-marrow dose [Home Office Scientific Research and Development Branch, 1985]. The LD_{50} value of 425 rads is considerably higher than about 300 to 325 rads, suggested by Lushbaugh [1969].

Our illustration of the OED only considers a constant dose rate. Accordingly, we have neglected the 150 rads for recovery by the human body from a dose received within a "short time." However, it should be noted that according to the suggested application of the OED

formula,* this will underestimate the accumulated LD_{50} dose by 150 rads. In order to express the total accumulated lethal dose as a function of dose rate rather than time, we assume a constant dose D_0, over various times t, yielding the constant dose rate $r = D_0/t$ (rads/h). We also choose the constant dose $d = r_0 t_0$ and solve for t giving,

$$t = \frac{r_0 t_0}{r} \quad \text{(h)} \; . \tag{20}$$

Then, since the OED formula is applicable for exposure periods greater than a few minutes, we choose $r_0 = 600$ (rads/h) and $t_0 = 1$ h, obtaining

$$\begin{aligned} X &= 450 + (10/24)\ (600/r) \\ &= 450 + (250/r) \quad \text{(rads)} \; , \end{aligned} \tag{21}$$

where r is the dose rate in rads per hour.

Other Data.

Data from other sources are also individually plotted in Fig. 7. The two values marked "R42" are based on the LD_{50} values given in the "Penalty Table" by the National Committee on Radiation Protection and Measurements [1974]. For one-week exposure, an LD_{50} value of 300 rads (450 R) is given; that corresponds to an average dose rate of about 1.77 rads/h (2.68 R/h). For one-month exposure, an LD_{50} value of 400 rads (600 R) is given; that corresponds to an average dose rate of about 0.55 rads/h (0.82 R/h).

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*"As a result of the application of this formula, the policy has been adopted that an Operational Equivalent Dose can be calculated by noting the dose registered on the dose meter and subtracting from this 150 plus 10 each day subsequent to the commencement of the exposure." [Home Office Scientific Research and Development Branch, 1985].

The two values marked "BIR" in Fig. 7 are based on information from the British Institute of Radiology (BIR) as quoted on p. 84 in the British Medical Association report of 1983.

The rectangles in Fig. 7 reflect dose and dose rate uncertainty and are based on the 1964 Mexican accident involving cobalt-60 γ-ray radiation exposure of five family members [Martinez et al., 1964] that resulted in four deaths (†) and one survivor (S).

DISCUSSION.

Plots of the protracted radiation response models show a considerable variation in accumulated lethal exposure dose versus dose rate. However, with the exception of the Bateman model, those plotted suggest a marked increase in LD_{50}, commencing with dose rates less than about 3 to 10 rads/h; the even more rapid increase in LD_{50} for dose rates from about 1 to 3 rads/h probably reflects cell proliferation. Since the Bateman model is based on a relationship that follows an inverse proportionality with the cube root of dose rate, the log-log plot in Fig. 7 shows that the Bateman model yields a more gradual increase with decreasing dose rate, compared with the other models.

A significant part of difference shown for the OED and Bateman ($K = 1.64$) models compared to the others plotted is attributed to the values assigned to the LD_{50} for the prompt or brief period of exposure, reflected at the high dose rate end of the plots in Fig. 7. That is, for the Bateman model ($K = 1.64$) the LD_{50} for high dose rate (600 rads/h) is 358 rads, and that chosen for the OED model is 450 rads. The other models plotted were normalized to 300 rads for prompt or high dose rate exposure with the exception of the Strandqvist model. For the Strandqvist model, a brief exposure means radiation dose accumulated within one week where the LD_{50} value is 345 rads. For an exposure period of one week, that value corresponds to an average dose rate of 2.05 rads/h. Furthermore, that model does not accommodate higher dose rates. LD_{50} values for a prompt or brief period of exposure used for the plots in Fig. 7 are summarized below.

Model	Prompt or Brief Exposure LD_{50} (rads)
Strandqvist	345 (one week, 2.05 rads/h)
Bateman, K = 1.64	300 rads (prompt); 358 rads (600 rads/h)
Bateman, K = 2.29	236 rads (prompt); 300 rads (600 rads/h)
Krebs and Jones	300 rads (600 rads/h)
ERD	300 rads (prompt)
OED	300 rads (600 rads/h)

Since we assume an LD_{50} value of 300 rads for a brief period of exposure, the corresponding normalizing dose rate of 600 rads/h chosen for model illustration is consistent with Krebs and Jones analysis of animal data where they suggest that an LD_{50} dose delivered in about 30 min or less ceases to be dose-rate dependent. Parameters specified to illustrate the models, such as A = 325 rads and m = 0.045 h for the linear portion of the Krebs and Jones model, are a consequence of the LD_{50} and dose rate values chosen. Other values chosen have the effect of specifying different parameter values which can alter the plots to some extent. We then conclude that additional investigation regarding parameter values of the various models is needed to more precisely predict accumulated LD_{50} for protracted doses.

The Strandqvist model, which is based on a simple power function relationship is a straight line on the log-log plot in Fig. 7. Compared with the other models, it appears to be an oversimplification with limited dose rate application. For a slope parameter of b = 0.26, it appears to considerably underestimate the LD_{50} dose-rate dependency. The Strandqvist plot with a slope parameter value of b = 0.52, a factor of 2 increase over b = 0.26, was indicated by clinical and accident studies of human blood cell responses [Yuhas, Stokes, and Lushbaugh, 1972]. However, that plot appears to considerably overestimate the accumulated dose that humans can tolerate when contrasted with the Mexican accident experience [Martinez et al., 1964]. In that accident, one family member survived the exposure, having received a somewhat lower average dose rate than the others.

The Strandqvist model appears to have limited application for military planning considerations, although various adjustments could arbitrarily be made in the two parameters--D_0 (single-dose requirement) and b--to produce a plot trend more in line with the other models.

The marked sensitivity of the Krebs and Jones model to the exponential repair parameter k is clearly illustrated in Fig. 7 for dose rates less than about 2 rads/h. Values of k greater than about 1.46 rads/h would be excessive, judged by the Mexican accident data. It is interesting to note, however, that both the Krebs and Jones model with a k value of 1.27 rads/h and the ERD model with a β value that corresponds to 2.5 percent/day are reasonably close over the dose range plotted. Also, the accumulated dose for the points at 0.82 and 2.68 rads/h, suggested by the BIR, are coincident with the Krebs and Jones model (k = 1.09 rads/h) and correspond to the ERD model at 2.68 rads/h. The tendency of the Krebs and Jones model (as well as the ERD model) to decrease in slope for dose rates between 0.1 and 1 rads/h appears to be a desirable feature of a protracted dose model, assuming that for increasingly smaller dose rates, continuous exposure to ionizing radiation could not be tolerated indefinitely. Of course, this slope trend is to be expected for the ERD model since it has a limiting LD_{50} value [see Eq. (16)] based on an irreparable damage component (10 percent as assumed here).

At the high dose rate end--several hundred rads per hour--the turning down of the Krebs and Jones curve is due to the linear portion of the model, which would actually appear as a straight line if this was a linear rather than a log-log plot. Where necessary, an adjustment could easily be made in that model to avoid a discontinuity where LD_{50} becomes independent of dose rate ($\geq$ 600 rads/h).

The Bateman model suggests increasingly larger tolerance to radiation with decreasing dose rate even for high dose rates. However, the overall curve is generally flatter at low dose rates when compared with the other models. In the ERD model, doubling the repair from 2.5 to 5 percent per day suggests increasingly larger tolerance for dose rates less than about 20 rads/h. Based on the Mexican accident data, this increased repair rate given by the β parameter appears

to be excessive. Also, when compared to the suggested NCRP [1974] 42 guidance values, it is not clear why there is such a large discrepancy between them and the ERD model, even for $\beta = 2.5$ percent/day, since presumably they were somewhat based on the ERD model. Some of the discrepancy could be attributed to a difference in the prompt or high dose rate LD_{50} assumed. The form of the OED model plotted in Fig. 7 depends only on the brief high rate of exposure and the recovery rate of 10 rads/day since we have neglected the initial biological recovery allowance of 150 rads contained in the OED formula. Even so, with the exception of the Bateman model, the OED model estimates a generally higher level of LD_{50} for dose rates from a few rads per hour to several hundred rads per hour. This is simply because the LD_{50} value of 450 rads for a brief high exposure rate dominates the accumulated LD_{50} over that range of dose rates. More importantly, the OED model, as indicated in Fig. 7, does not limit the accumulated exposure dose with decreasing dose rate; as discussed, this is not a desirable feature of a protracted dose model particularly for extended exposure periods of many months.

This brief review of some suggested models of protracted radiation response that are based on the lethality endpoint illustrates the need for additional investigation. Further study should precede a system analysis approach to modeling protracted radiation response for application to military operations and planning. Even though lethality is only ore of the endpoint responses of interest in casualty considerations, the models do predict various degrees of biological recovery. However, based on our review, we find that both the Krebs and Jones model and the ERD model appear to be the most promising. The four-parameter Krebs and Jones model, although somewhat complex, is flexible and appears to simulate the expected trend of accumulated dose with decreasing dose rate reasonably well. The three-parameter ERD of similar complexity, is also flexible and provides the expected trend of accumulated LD_{50} against dose rate. However, for our purposes (in which we transform the independent variable from time to dose rate), the ERD model has the disadvantage

of being transcendental where a nonlinear solution is required for the accumulated LD_{50}.

Better substantiation of any selected model should be based on a more in-depth analysis of available data from animal studies and human experience; for example, the Juarez, Mexico, accident involving exposure to cobalt-60 γ-ray radiation from a discarded radiotherapy unit [Marshall, 1984] can yield still more information. Also, our comparisons of the protracted radiation exposure models here are based on continuous and constant exposure rate levels because data on arbitrary exposure periods and/or varying dose rates are scarce or limited in scope. However, as Krebs and Jones [1975] imply, when average daily dose rates are less than about 2.6 rads/h (or about 62 rads/day), the exposure history for the 24-h period is largely irrelevant.

Through further investigation, it should be considered whether utilizing the kinds of models reviewed here would be appropriate to express biological recovery for interrupted periods of exposure and time-varying dose rates. Indeed, some system analysis studies have taken that approach [Davidson, 1957; Knapp, 1965; and Schmidt, 1981].

Additional investigation is also required to choose whether the kinds of models reviewed here, or modifications of them, can be applied to other endpoints such as prodromal responses. Although it is unclear whether these models can adequately be applied to the prodromal symptomatology for protracted radiation, some studies have done so [Knapp, 1965; and Schmidt, 1981]. However, because the kind of biological recovery illustrated in this review may not adequately model other processes (such as a physiological clearing action, perhaps combined with repair), a different type of modeling approach may be necessary to accommodate prodromal responses to protracted radiation. For example, for dose rates in the therapy range of about 1 to 30 rads/min (60 to 1800 rads/h), there are indications that nausea and vomiting depend more on the total accumulated dose than on the dose rate [Baum et al., 1984]. This review of existing models of protracted radiation based on lethality as the endpoint reveals the need for additional investigation which should precede a system analysis approach for application to military operations and planning.

SECTION 5

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